REMARKS

I. Status

Claims 35-42 are pending and rejected. Claim 35 has been amended to recite "cartilage disease" and to revise the group of specific disease recited. Claims 37-39 have been amended to independently recite the definitions of R^1, R^{1-1}, R^{1-2}, and R^{1-3}. Claims 40-42 have been amended to delete the recitation of "of claim 38."

No new matter has been introduced. Entry and consideration of the amendments are respectfully requested.

II. Statement of Substance of Interview

Applicants appreciate the courtesy of a telephone interview between Examiner Frazier and the undersigned on September 19, 2011.

Applicants proposed amending claims 37-39 and 40-42 to overcome the claim objections and rejections under § 112. The Examiner indicated that the amendments to recite the definitions of R^1, R^{1-1}, R^{1-2}, and R^{1-3} in the independent claims and to delete the recitation of "of claim 38" would obviate the objection and rejections.

Also, Applicants proposed to amend claim 35 to replace the phrase "cartilage-related disease" with "cartilage disease" and to remove "injury by sports and keypuncher's disease" from the last line of the claim. Further, Applicants explained the differences between the method of the amended claims and the references of record. No agreement with respect to the claims was reached.

It is respectfully submitted that the present Statement of Substance of Interview complies with the requirements of 37 C.F.R. §§ 1.2 and 1.133 and MPEP § 713.04.

II. Response to Claim Objections

Claims 41 and 42 are objected to under 37 C.F.R. § 1.75(c) as being in improper multiple dependent form. Claims 40-42 have been amended to delete the phrase "of claim 38." Reconsideration and withdrawal of the rejection are respectfully requested.

III. Rejection under 35 U.S.C. § 112

A. Claims 37-42 are rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention.

The Examiner states that the feature of "wherein all symbols have the same meanings as those described in Claim 35" recited claims 37-39 makes it unclear as to whether claims 37-39 are intended to be independent.

Claims 37-39 have been amended to independently recite the definitions of R^{1}, R^{1-1}, R^{1-2}, and R^{1-3}. Reconsideration and withdrawal of the rejection are respectfully requested.

B. Claims 40-42 are rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention.

The Examiner asserts that claims 40-42 do not have antecedent basis for the phrase "the composition of claim 38." Claims 40-42 have been amended to delete the phrase "of claim 38." Reconsideration and withdrawal of the rejection are respectfully requested.

IV. Rejection under 35 U.S.C. § 103

A. Claims 35-42 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Cameron et al (WO 98/27976, previously cited) in view of Tani et al (US Patent 6,110,969, previously cited), and optionally further in view of Anastassiades (US Patent 6,133,230, previously cited) and/or Constan (WO 2004/078169).

The rejection should be withdrawn for the following reasons.

(1) The cited references do not teach or suggest the claimed methods. For example, the cited references do not teach or suggest the method for treating cartilage disease as recited in amended claim 35.

The currently amended claim 35 recites "treating cartilage disease" including "rheumatoid arthritis, osteoarthritis, cartilage damage, articular disk damage, meniscus injury, chondrodysplasia, achondroplasia, achondrogenesis, dyschondrogenesis, chondrodystrophia, articular chondrocalcinosis, acute purulent arthritis, tuberculous arthritis, syphilitic arthritis, systemic lupus erythematosus, spondylosis deformans, and disk herniation."

These cartilage diseases are all related to cartilage damage and are totally different from the condition which presents with low bone mass or skeletal disorders of Cameron. In the present application, the compound of general formula (I-1) stimulates chondrogenesis, inhibits the calcification of cartilage by inhibiting osteopontin expression and thus treats the above diseases.

The present invention is for the maintenance of the flexibility and viscoelasticity of cartilage by stimulating chondrogenesis and further inhibiting cartilage calcification. These functions or effects cannot be obtained by bone formation or bone mass increase as described in

Cameron for the reasons described below. As such, one skilled in the art would not have been motivated to modify the teachings of Cameron to reach the claimed invention, with reasonable expectation of success or reasonable predictability.

Bone is a very rigid tissue and protects internal organs as well as serves as a rigid structure to the human body. On the other hand, cartilage, which covers the ends of bone, is a smooth, tough, resilient, and protective tissue composed of collagen, water, and proteoglycans. And cartilage has a role to reduce friction among bones as a joint moves, which is different from the role of bone. Correspondingly, cartilage diseases are different from bone diseases, and treatment of cartilage diseases is different from treatment of bone diseases.

Exhibits A and B (submitted March 17, 2010) show that, in a joint, cartilage at the ends of bone plays a role like a cushion for bone, and its flexibility and viscoelasticity are the functions specific to cartilage. Thus, damage to or hardening of cartilage leads to the loss of flexibility and viscoelasticity which are a characteristic of cartilage and becomes a cause of the cartilage-related diseases cited in the amended claims.

For example, hardening of subchondral bone, osteophyte formation and the like are observed in osteoarthritis accompanying the change in which cartilage viscoelasticity is lost by metabolic abnormality of cartilage matrix. Also, it is known that osteophyte is formed when marginal bone of a joint overgrows. See, Exhibits C and D (submitted March 17, 2010).

In addition, for example, as described at lines 4-15 on page 9 of the present specification, articular chondrocalcinosis is a typical disease caused by abnormality in cartilage calcification, and the calcification of cartilage leads to the loss of cartilage flexibility and to the loss of its function.

The above diseases accompanied by cartilage disorder cannot be treated by increasing bone mass. In the treatment of the above diseases, it is of course necessary to stimulate chondrogenesis. In addition, it is also necessary to maintain cartilage flexibility by inhibiting the calcification and hardening of cartilage and to maintain its function as cartilage in order to bend and extend a joint.

On the other hand, in Cameron, the EP2 agonist increases bone mass and treats the condition of low bone mass, such as osteoporosis or bone fracture. In contrast, the diseases recited in the amended are not conditions of low bone mass and thus cannot be treated by increasing bone mass. Also, Cameron describes the bone formation, but does not describe cartilage formation, much less describe or mention the effect of inhibiting cartilage calcification.

Applicant notes that the Examiner asserts that "Cameron et al do teach that the mammal to be treated may present with low bone mass or other skeletal disorders and that the compound used may be applied to the cartilage growth plate, and therefore one skilled in the art would reasonably expect that the subject would be in need of stimulating chondrocyte growth in order to form new bone tissue" at lines 15-19 on page 5 (paragraph 8) of the Office Action. However, the applicants believe that one skilled in the art *would not be able to reasonably predict the recited function (stimulating chondrogenesis) at the administration locus (the cartilage growth plate)* for the reasons as presented above and supported by technical references. Further, the diseases recited in the amended claims are not treated by bone formulation, and it is predicted that the above diseases deteriorate rather than improve when new bone is formulated, that is, ossification of cartilage is promoted and the cartilage flexibility is lost.

Therefore, Applicant respectfully submits that one skilled in the art would not have been motivated or guided to reach to the idea of cartilage formation and effect of inhibiting cartilage

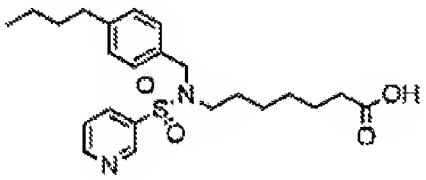
calcification of the present invention from the disclosure of Cameron. Instead, Cameron *teaches away from the present invention because of the deterioration of cartilage function and deterioration of the above diseases* by cartilage hardening are predicted.

(2) The cited reference, either alone or in combination, is not an enabling disclosure for one of ordinary skill in the art to practice the claimed methods.

Cameron describes an enormous scope of the compound represented by Formula I on pages 7-36. Further, Cameron does not describe specific production methods for these compounds, and specific examples of the compounds are limited to the 9 compounds described in Example 1 on pages 77-78. There is no specific description about the production methods and the references for these compounds. Further, no data of the EP2 agonistic activity of the Example compounds is provided, and no data relating to bone fracture, which is the main subject of Cameron, is described. Importantly, there is no teaching or suggestion of any experimental method regarding cartilage repair, to which the present methods are directed.

Accordingly, Applicants submit that Cameron, either alone or in combination, does not describe the claimed methods sufficiently enough to enable one of ordinary skill in the art to carry out the invention, and thus cannon sustain the rejection.

(3) Further, all the compounds described in Example 1 of Cameron are sulfonamide derivatives, illustrated as follows.



Such sulfonamide compounds have totally different structures from the compounds of the present invention. Accordingly, one of ordinary skill in the art would not have applied a structurally dissimilar compound to the teaching of Cameron, as suggested in the Office Action, to treat cartilage diseases, which are not described at all in Cameron.

Reconsideration and withdrawal of the rejection are respectfully requested.

B. Claims 35-42 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Constan et al. (WO 2004/078169) in view of Tani et al. (Bioorg. Med. Chem., 10(4), pp. 1107-1114, 2002) (referred to as "Bioorganic" for clarity).

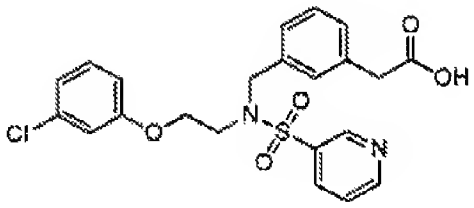
The rejection should be withdrawn for the following reasons.

(1) The cited reference, either alone or in combination, is not an enabling disclosure for one of ordinary skill in the art to practice the claimed methods.

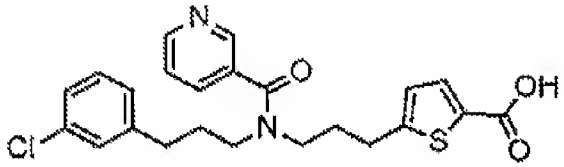
Constan teaches the use of the subject EP_2 selective receptor agonists with only a cursory mention of facilitating cartilage repair (and each mention is in an identical general summary statement of the invention on pages 1-2, 6, and 25). That is, Constan is directed to the use of EP_2 selective receptor agonists in general and does not teach particular use for treating cartilage-related disease.

More specifically, Constan merely mentions cartilage repairing in general, but no data regarding cartilage repairing is described, and no method for measuring any cartilage repair-facilitating effect is taught or suggested in Constan. Accordingly, Applicants submit that Cameron, either alone or in combination, does not describe the claimed methods sufficiently enough to enable one of ordinary skill in the art to carry out the invention, and thus cannon sustain the rejection.

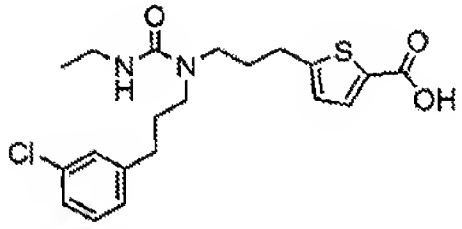
(2) Further, Constan describes Formula I having a very broad scope, but does not include the compounds of the present application (or the compounds described in Bioorganic). Specifically, the compounds described in the Example of Constan are sulfonamide derivatives such as Example 2,



amide derivatives such as Example 5, and



ureide derivatives such as Example 7



, which are structurally different from the compounds of the present application.

Such compounds have totally different structures from the compounds of the present invention. Accordingly, one of ordinary skill in the art would not have applied a structurally dissimilar compound to the teaching of Constan, as suggested in the Office Action, to treat cartilage diseases. Reconsideration and withdrawal of the rejection are respectfully requested.

In view of the above, allowance of this application is now believed to be in order, and such actions are hereby solicited. If any points remain in issue which the Examiner feels may be

best resolved through a personal or telephone interview, the Examiner is kindly requested to contact the undersigned at the telephone number listed below.

The USPTO is directed and authorized to charge all required fees, except for the Issue Fee and the Publication Fee, to Deposit Account No. 19-4880. Please also credit any overpayments to said Deposit Account.

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